Review Article

Post-COVID lung disease(s)

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Abstract:

Post-COVID lung impairment and diseases are major public health concern in the pandemic of COVID-19. Multiple etiological factors can lead to post-COVID respiratory symptoms, with post COVID fibrosis or diffuse parenchymal lung disease being the major concern. We searched PubMed database for English literature related to post-COVID lung disease and we summarized the existing evidence on radiological, physiological, and histopathological aspects of post-COVID lung diseases. We suggest a guidance on the evaluation of these patients and highlight management considerations including general care, pulmonary rehabilitation, and lung transplantation. We also explain gaps in knowledge and awaited ongoing research results, especially in the field of drug therapies including corticosteroids and antifibrotics.

Keywords:

Acute respiratory distress syndrome, antifibrotic therapy, COVID-19, interstitial lung disease, pulmonary fibrosis, pulmonary rehabilitation

By the end of January 2022, SARS-CoV2 has caused more than 360 million confirmed cases and more than 5 million deaths worldwide according to the World Health Organization data.[1] Data accumulated over the past 2 years on the epidemiology, diagnosis, and treatment of this new disease with exponential increase in scientific publications and worldwide collaboration in research on the management of the acute infection, still the long-term health effects on survivors of COVID-19 are unknown. Due to the scale of pandemic and the large population affected, postacute sequelae of COVID-19 including respiratory complications will be a significant public health program with feared risks of disability, decreased quality of life, and increased health-care burden. In this review, we summarize and analyze what is known so far on the epidemiology and natural history of lung disease(s) after acute COVID-19 disease, the clinical, radiological, and physiological manifestations, and the current management of the disease.

Search Methodology

We searched PubMed database using keywords "post-COVID lung disease," post-COVID fibrosis," "post-COVID pulmonary function," and "post-acute sequalae of COVID-19 "for English language articles. After abstract screening, the full text of relevant articles was reviewed by all authors. Additional articles were identified from the references and from similar articles feature. Original manuscripts reporting on medium to long-term follow-up after acute COVID-19 disease (>4 months) were selected. Data related to pulmonary impairment including clinical, radiological, and physiological tests were selected. In addition, review articles, national and international guidelines and position statement papers and opinion/viewpoint papers on treatment theories and recommendations were selected and reviewed. Isolated case reports were excluded.

Lung Impairment in Prior Viral Pandemics

In the absence of long-term data after COVID-19 which is a new disease,

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longitudinal studies after acute respiratory distress syndrome (ARDS) and after other viral pandemics (Influenza, SARS, and MERS-Cov) can inform on the potential of evolution of lung impairment after COVID 19. Multiple longitudinal studies followed up ARDS survivors.[2-6] Wilcox *et al*.[5] reported on follow-up of severe ARDS survivors after 5 years. They found minor persistent radiological changes with dyspnea mostly attributed to deconditioning and myopathy rather than fibrotic lung disease. Comparable results were found by Ngai *et al*.[3] in young patients with ARDS. Survival bias is possible here with the risk that patients with significant lung impairment died earlier.

Similar results were observed after severe influenza ARDS in the H1N1 pandemic with a pattern of reduced DLCO with minor residual abnormalities and lack of progressive fibrotic disease, even in patients requiring extracorporeal membrane oxygenation with radiological changes consisting of fibrotic bands and septal lining.[6]

Less data are available after SARS and MERS infection. However, available reports demonstrated persistent abnormalities up to 6-year postinfection including mainly decreased DLCO but also restrictive lung disease. Persistent radiological abnormalities included both inflammatory Ground-glass opacities (GGO) and fibrotic patterns (traction bronchiectasis and fibrotic bands).[2]

Respiratory Symptoms Burden after COVID19

Acute SARS-CoV2 infection can range from asymptomatic or mild flu-like illness to severe ARDS and death, but a substantial proportion of patients will still suffer from long-term symptoms that can last for weeks or even months.

A nationwide study done in the UK with 3290 responders, among which only 17% were hospitalized, showed that 40% of patients had 5–6 persisting symptoms after COVID-19 infection. Breathing problems, fatigue, muscle weakness, and joint pain were the most frequently reported symptoms. Patients having a history of pulmonary disease were more likely to have post-COVID-19 breathing problems. No significant difference in symptoms prevalence was present regardless of the hospitalization status.[7]

Another study which included 2113 patients who did not require intensive care unit (ICU) admission reported that on average six symptoms persisted after COVID-19 infection with fatigue and dyspnea being the most prominent ones after 3 months. Less than 1% of patients had no residual symptoms. In the same study, 85% of the responders reported having a good health status before COVID-19 infection. Only 7.2% reported a good health status 3 months after COVID-19 infection.[8]

A large multicentric study done in Spain on 1142 hospitalized individuals showed that 61% experienced fatigue and 55% suffered from dyspnea at activity 7 months after discharge, with dyspnea at rest being present among 23.5% of patients. Patients who required ICU admission were more likely to suffer from limitation of occupational activities as well as moderate-to-severe impairment in daily living activities. The number of preexisting comorbidities and symptoms at hospital admission as well as female gender were risk factors associated with the existence of dyspnea or fatigue 7 months after hospital discharge.[9]

Persistent respiratory symptoms in individuals post-COVID 19 likely have different and sometimes coexisting etiologies [Figure 1] depending on the preexisting comorbidities, course of the acute COVID-19 disease, length of ICU, and hospital stay. Interstitial lung disease (ILD) or residual fibrosis is one component, in addition to deconditioning and neuromuscular weakness, thromboembolism, cardiac injury, anxiety, mental health disease as well as central hyperventilation. In ICU, survivors' symptoms likely overlap with post-intensive care syndrome that is not specific to COVID-19 and frequently affects ARDS and critical illness survivors.

Pathophysiology of Post-COVID Lung Disease

Pulmonary fibrosis can be a pathological outcome of acute lung disease associated with abnormal healing after viral or bacterial lung infections. Viral mediated epithelial injury leads to replication of alveolar Type II cells and transforming growth factor (TGF-β) secretion that is thought to meditate lung injury and fibrosis by inducing differentiation of fibroblast to myofibroblast

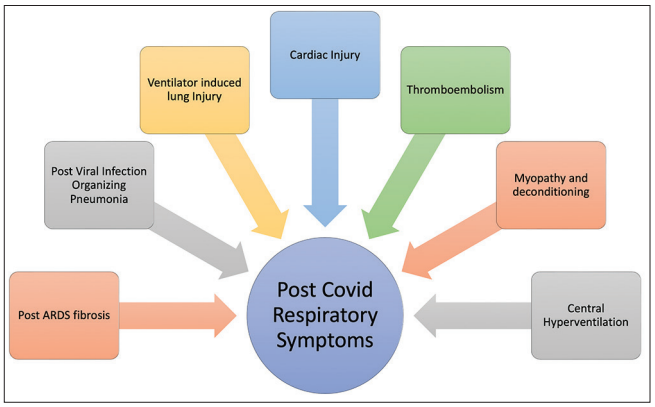

Figure 1: Etiologies of persistent respiratory symptoms post-COVID-19. ARDS: Acute respiratory distress syndrome

and deposition of extracellular proteins and fibrils.[10] The fibrotic process is also fueled by megakaryocyte activation in the lung microvasculature leading to fibroblast growth factor and TGFb secretion.[11] Mechanical ventilation can increase the expression of TGF-beta perpetuating the cycle of fibrosis which explains of fibrosis in critically ill and mechanically ventilated patients.[12]

Autopsy samples showed that exudative diffuse alveolar damage was the most prominent finding on pathology during the early stages of COVID-19 infection.[13]

Postmortem biopsies showed specific pathological changes in the exudative phase and in the proliferative phase. Hyaline membranes, alveolar and interstitial infiltration by macrophages and lymphocytes, interstitial edema, viral cytopathic changes, and fibrinous airspaces exudates were more common in the first and early phase. Squamous metaplasia, interstitial fibrosis, intraalveolar fibrin plugs were prominent in the second and late phase of ARDS.[14]

Most of the studies assessing pathological changes were autopsy studies, whereas a new study showed that the most common pathological finding from surgical lung biopsies taken from patients post-COVID was usual interstitial pneumonia and it was present in 9 out of 18 individuals, of whom 2 had ongoing acute lung injury. Patients with UIP tended to be older than patients not showing a UIP pattern, and patients with UIP tended to have GGOs associated with interstitial thickening and peripheral reticulations, whereas patients without UIP tended to have only GGOs.[15]

Organizing pneumonia, lymphoplasmacytic interstitial cell infiltrates with or without giant cells were found in 30 out of 50 transbronchial cryobiopsy samples in patients who recovered from COVID and who had imaging findings or pulmonary function test (PFT) findings suggestive of Diffuse ILD. Fibrotic patterns observed in usual and nonspecific interstitial pneumonia were not observed, but fibrotic patches mostly due to old organizing pneumonia were reported.[16]

Differences of histopathological findings between studies are likely related to sampling at various stages of diseases and different disease severities (postmortem vs. follow-up in survivors).

Radiological findings in the follow-up of patients with COVID19

Patients recovering from acute COVID-19 have residual computed tomography (CT) abnormalities of different severities. The pattern of radiological findings is classified into persistent inflammatory (ground-glass abnormalities (GGO), peripheral consolidations) or fibrotic (fibrotic bands, traction bronchiectasis, and honeycombing). These patterns are dynamic and frequently overlap and coexist.

Ground glass opacities were the most common abnormalities found on CT scans in the early post-COVID infection period, with fibrotic lesions or bands increasing in prevalence during the follow-up period. Morin *et al*. found that 63% of the 478 patients included in his study had residual GGO 4 months after COVID infection and that fibrotic lesions were only present in 19% of individuals mainly those who received a diagnosis of ARDS.[17] One study of 137 patients found residual GGOs in 75% of them, 3 months after COVID infection and fibrotic lesions in 18% of included patients, the study participants had an average body mass index (BMI) of 27 kg/m^2 and 32% of them needed invasive ventilation, which may explain the high proportion of residual imaging findings.[18]

In patients who were hospitalized with severe and critical COVID-19 infection 72% still had GGOs 6 months after COVID-19 infection with fibrotic bands increasing in prevalence between initial CT scans done during acute COVID-19 and follow-up CT scan.[19]

Most of the residual imaging manifestation post-COVID-19 tends to regress. Of 73 individuals included in a study by Vijayakumar *et al*., 41 of them had GGOs and fibrotic bands at 3 months but only 16% of patients had residual abnormalities at 1 year with none of the patients showing the progression of imaging abnormalities.[20]

Liu *et al*. found that in patients with moderate and severe COVID-19 infection, interlobular septal thickening and fibrotic bands were more prevalent than crazy paving pattern and GGO at discharge. Radiological resolution reached 42% and 75% at 1 month and 6 months after acute COVID-19 infection, respectively.[21]

Risk factors for persistent imaging findings of COVID-19 were increased hospital stay and a BMI of more than 30 kg/m^2, need for invasive or noninvasive mechanical ventilation, increased age, and elevation of certain biomarkers such as C-reactive protein, lactate dehydrogenase, and fibrinogen on initial presentation.[20,22]

CT angiography is sometimes used to assess for coexistent thromboembolism as a cause of persistent symptoms such as dyspnea. Its use is not routine but likely indicated in whom the plain radiological findings do not explain the symptoms or in patients with new-onset or worsening symptoms after improvement. Fifty-five patients with residual symptoms had a

CT angiography 3 months after COVID-19 infection that showed the presence of pulmonary embolism among only three of them with none of these three patients receiving preventive anticoagulation during hospitalization.[23]

Pulmonary function tests

Pulmonary function tests have always been valuable in assessing pulmonary diseases and respiratory function. Experience from previous pandemics such as MERS and SARS has shown that pulmonary function testing is a valuable tool to assess for lung damage after recovery.

It has been shown that diffusion abnormalities are present after the COVID-19 acute infection.

Out of 224 patients who had pulmonary function testing 4 months after acute COVID-19, a DLCO of <80% of the predicted value was found in 51% of them, only 28 patients included in this study were admitted to the ICU, and only 21 required mechanical ventilation.[24]

Diffusion abnormalities tend to regress with time but may not return to normal.

Wu *et al*. showed that mean DLCO increased from 76% to 88% of the predicted value at 6 and 12 months after acute COVID-19. However, 33% of participants had a DLCO <80% of the predicted value at 12 months. Further studies are needed to assess the regression of diffusion abnormalities beyond 1 year after COVID-19 infection. Six-min walking distance increased from 535 meters at 3 months to 615 meters at 1 year.[25] Similar diffusion abnormalities were also found in other studies.[26]

Pulmonary function testing results consistent with restrictive patterns were also reported

Munker *et al*. found a decrease in forced vital capacity, total lung capacity (TLC), forced expiratory volume 1, and DLCO, 4 months after COVID-19 infection. No difference in lung function parameters was found between patients who still had residual symptoms due to COVID-19 infection and nonhospitalized patients. Gas exchange abnormality on exercise was also found in patients with mild disease. However, the clinical significance of this finding remains to be elucidated.[27] Other smaller studies showed similar abnormalities on pulmonary function testing, that could also be consistent with a mild restrictive pattern.[28-30]

In the same study by Wu *et al*., six-min walking distance increased from 535 m at 3 months to 615 m at 1 year.[25]

Risk factors for diffusion and restriction impairment on PFT 1 year after recovery were female sex, chronic kidney disease, mechanical ventilation, smoking status, residual CT abnormalities, and length of hospital stay.[27]

While new-onset obstructive airway disease from bronchiolitis, new onset Asthma or bronchiectasis is always a concern, this was not found in most longitudinal studies. In Finland, twenty patients who had severe COVID or were admitted to the ICU did not show any dysfunctional small airways 6 months after COVID-19 infection.[31]

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) results can provide insight on the causes of exercise limitation in patients with persistent symptoms, especially when multiple etiologies coexist. Deconditioning and hyperventilation syndromes[32-34] are two important causes in some published studies. These results are not generalizable as in general patients referred for CPET are fit enough to exercise, usually not on oxygen therapy and do not have severe limitations increasing the potential for selection bias. Nevertheless, the CPET results could inform further management and patient education in a subset of patients with persistent symptoms.

A study by Rinaldo *et al*. on 75 patients in which more than half of the patients experienced severe or critical illness found that the only PFT abnormality was a decreased DLCO. This study also found that 55% of patients had a low peak oxygen consumption (V O2) probably related to deconditioning in the context of a prolonged hospital stay particularly in the severe and critical cases and in those who developed viral myopathy. Patients with preserved exercise capacity had normal peak oxygen consumption levels.[35]

Hyperventilation was the second-most common cause of exercise limitation in a study which involved 114 patients 3 months after COVID-19 infection. Hyperventilation was equally prevalent among patients with decreased and preserved diffusion capacity.[36]

One hundred and fifty-six individuals were assessed for exercise capacity 3 months after COVID-19. Forty-seven percent of them had a reduced peak oxygen consumption which was more prominent in patients admitted to the ICU. This finding was mainly related to deconditioning.

Circulatory factors were the second-most common cause of exercise limitation, followed by ventilatory inefficiency present in one out of seven patients due to perfusion/ventilation mismatch and dysfunctional breathing patterns such as hyperventilation. Individuals with dyspnea on the follow-up appointment had a lower ventilatory efficiency, heart rate, and systolic blood pressure.[37]

Three months after recovery from COVID-19 infection, no difference in the rate of patients with reduced exercise capacity and low peak O2 consumption was found whether acute COVID-19 infection was mild, severe, or critical. This finding is mostly due to the phenotypical heterogeneity of acute COVID-19, and viral mechanisms of lung injury which are not yet clarified. Increasing COVID-19 infection severity could increase the rate of dysfunctional breathing patterns such as hyperventilation.[38]

Disease phenotypes

To summarize the most common pattern of lung disease after severe COVID-19 is characterized by persistent GGOs and fibrotic bands with residual mild restrictive pattern and diffusion capacity abnormalities. Other possible disease phenotypes include organizing pneumonia and severe fibrosis. One-year outcomes are characterized by stability or regression of the abnormalities without clear indications of progressive fibrosis. Longer follow-up data are eagerly awaited. In addition to interstitial pneumonia, thromboembolism, deconditioning and myopathy, cardiac injury, anxiety, and dysfunctional breathing should also be considered as possible etiologies of persistent dyspnea.

Evaluation and Management of Post COVID19 Lung Impairment

Patients with lung impairment after moderate-to-severe COVID-19 are currently mostly managed collectively as a chronic lung disease without specific or disease-modifying treatment. Since the available data so far showed improvement or stability in lung parenchymal findings over time without progressive fibrosis, observation with rehabilitation seems appropriate to most patients who survive the acute phase and can live without mechanical ventilatory support. When liberation from ventilatory or extracorporeal support is not possible, lung transplantation, discussed further later, is a viable option.

Nevertheless, we recommend multidisciplinary management of all patients who survive moderate to severe COVID 19, when possible, in a dedicated post-COVID clinic. The multidisciplinary team is expected to address mental cognitive and physical symptoms including respiratory symptoms.

The evaluation for post-COVID lung disease is summarized in Figure 2. All patients hospitalized for COVID-19 should be screened for persistent signs and symptoms of pulmonary disease (shortness of breath, exercise limitation, and hypoxemia) 4–6 weeks after their initial infection. In patients with persistent or progressive symptoms, baseline evaluation includes lung imaging (high-resolution CT when possible), lung function tests, and 6-min walk test). Upon clinical suspicion other potential etiologies should also be entertained including pulmonary thromboembolism, pulmonary hypertension, heart failure, preexisting undiagnosed ILD, or airway disease. Hence, the baseline investigations can be supplemented by echocardiography, cardiopulmonary examination test or CT angiography of the pulmonary arteries. General recommendations for patients with chronic lung disease apply to patients with COVID lung disease including vaccination (COVID, influenza, and pneumococcal), counseling for smoking cessation and nutritional and weight management. Specific suggested that treatment options are discussed next.

Pulmonary Rehabilitation

A comprehensive rehabilitation program including pulmonary rehabilitation is recommended in the acute hospital setting[39,40] and after hospitalization for moderate to severe COVID 19.[40-42] Multiple observational cohorts showed benefits in exercise capacity, pulmonary function, and health-related quality of life.[43-46] Low-intensity aerobic exercises followed by the introduction of strengthening exercises and formal occupational therapy and psychology evaluation. The European Respiratory Society and American Thoracic Society interim guidance recommended formal assessment 6–8 weeks after acute infection, a comprehensive pulmonary rehabilitation programs for patients with new or persistent respiratory symptoms in addition to oxygen requirements, persistent radiological abnormalities, or pulmonary function tests abnormalities.[40,47] Telerehabilitation and home-based programs are increasingly used,[41,48] especially with the restrictions due to the pandemic and the limited capacity of hospital-based programs. For example, a telerehabilitation program delivered through smartphone was shown to improve functional exercise capacity, lower limb muscle strength, and physical quality of life in a randomized clinical trial in China.[49] Telehealth programs can also improve accessibility for disadvantaged people, people from rural areas, and patients who cannot afford transportation.

Finally, as minorities and marginalized people are disproportionally affected by COVID-19, rehabilitation programs should ensure accessibility of these minorities including individualized education modules, multiple languages, and taking into consideration transportation and socioeconomic status.

Antifibrotic drugs

Pirfenidone and nintedanib are two antifibrotic drugs approved for use in idiopathic pulmonary fibrosis based on Phase III trials that showed slowing of

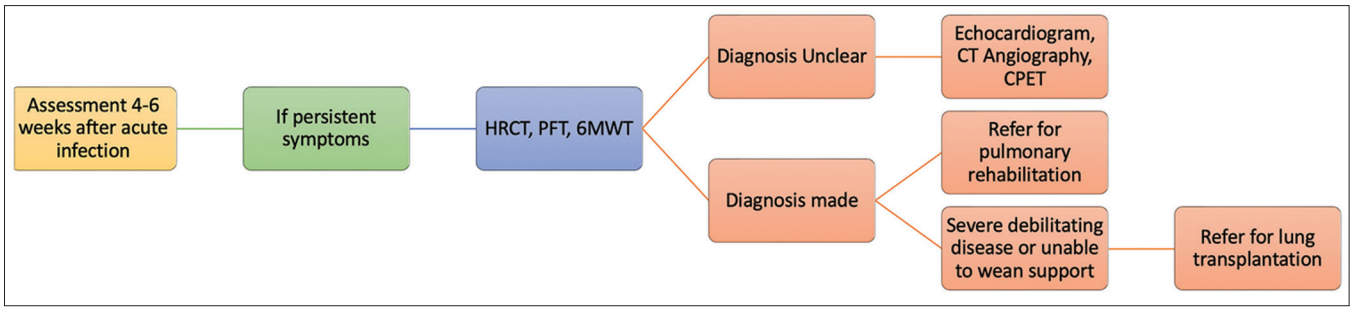

Figure 2: Respiratory follow-up of patients with COVID19. HRCT: High-resolution computed tomography, PFT: Pulmonary function tests, 6MWT: 6-minute walk test, CPET: Cardiopulmonary exercise test

disease progression.[50,51] Nintedanib was also shown to be beneficial in progressive fibrosing ILDs including scleroderma, connective tissue disease-ILD, and sarcoidosis. There is scientific rational to evaluate the benefit of antifibrotics drugs during or after moderate-to-severe COVID-19 pneumonia as early therapy might mitigate fibroblast activation and prevent fibrosis, also these drugs have some anti-inflammatory and antioxidants effects. In a small study in Japan, 30 patients with severe COVID-19 requiring intubated were treated with nintedanib and compared to historical control.[52] The 28-day mortality was the same, but the duration of mechanical ventilation was shorter.[52] Given the scale of the pandemic and the substantial number of patients who will be candidates for treatment, the available data are at most hypothesis generating. Moreover, in the authors opinion, antifibrotics drugs should be used only in the setting of a clinical trial unless a preexisting fibrosing ILD is reasonably suspected.

Prolonged steroid treatment

Prolonged steroid therapy beyond the acute phase treatment was suggested to treat possible evolution into organizing pneumonia. This is supported by follow-up imaging as described above and histological data reporting organizing pneumonia pattern on cryobiopsies. Dhooria *et al*.[53] (ref) randomized 120 patients 3–8 weeks after acute COVID to two prednisolone regimens, one that starts with 40 mg of prednisolone tapered over 6 weeks (called high dose group), the other low dose group (10 mg daily) for 6 weeks. Patients included were adults symptomatic with >20% radiological involvement. They observed no difference in the rate of complete radiological resolution or other secondary outcomes. The absence of placebo group is the main limitation in this trail. Myall *et al*.[54] (ref) selected patients for corticosteroid therapy if they stopped improving over time or worsened had evidence of ILD on imaging out of 837 patients screened they selected only 30 patients to receive corticosteroids (0.5 mg/kg of prednisolone) with a rapid taper over 3 weeks and they reported improvements in symptoms, radiological findings, and pulmonary function tests. In the absence of control group in this study, it is not to draw hard conclusions on the treatment effect of steroids versus natural history of post-COVID disease. Furthermore, organizing pneumonia histological findings can be found after bacterial pneumonias and do not usually require steroid treatment similar to the cryptogenic organizing pneumonia disease. Furthermore, prolonged steroids therapy in post-COVID patients carries substantial risks of immunosuppression, muscle weakness, and metabolic derangement in a population with metabolic comorbidities at baseline, already treated by immunosuppression in the acute phase and suffering from deconditioning after the hospital stay. Moreover, as described earlier, most patients are consistently improving without specific therapy. In the authors opinion and until randomized studies are published the use of corticosteroids, if any, should be limited to the subset of patients with clear worsening after recovery, evidence of inflammation on imaging and laboratory results and after exclusion of a new infectious or thromboembolic process.

Lung transplantation

COVID-19 patients with advanced fibrosis after ARDS with failure to wean from mechanical ventilation or extracorporeal support are offered lung transplantation in centers with this capacity.[55,56] Accumulating evidence from case series reported short term success and weaning off mechanical support.[56] The procedure is technically challenging, with severe pleural adhesions, hilar lymphadenopathy, and increased intraoperative transfusion requirements.[56] No cases of recurrence in the allograft were reported. Young age, absence of significant preexisting comorbidities, or multiorgan failure is usually prerequisites. While the indication for lung transplantation may seem clear patient evaluation and preparation including commitment to post lung transplantation immunosuppression and follow-up, psychological evaluation preoperative, details on family and social support are often lacking. With an added ethical challenge on whether patients who intentionally refuse vaccination should be offered such treatment

option. The indication is rather more challenging and controversial in patients who are still oxygen dependent with significant exercise limitation but are weaned off mechanical support given the natural history of the disease and the potential for improvement later. A period of observation is reasonable before deciding on lung transplantation on these patients.

Limitations

This review is limited by the available data so far, longer term follow-up is needed to define post-COVID lung diseases phenotypes and therapeutic trials are eagerly awaited. We included only English language literature manuscripts and only searched PubMed database; hence, there is a possibility we missed some published manuscripts related to the topic.

Conclusion

Persistent respiratory symptoms are common postacute sequelae of COVID19, and they are multifactorial. Persistent radiological abnormalities and fibrotic changes as well as lung function abnormalities including restrictive pattern and low diffusion capacity are common, especially after severe and critical disease but are usually stable, without progression and tend to improve with time. The burden of added disability and mortality in the long term remains to be elucidated. After ruling out thromboembolism and cardiac etiologies, pulmonary rehabilitation is recommended for most patients. Lung transplantation is suggested in severe disease. The potential role of antifibrotic therapy or prolonged steroids therapy needs confirmation by ongoing research.

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Conflicts of interest

There are no conflicts of interest.

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